Preliminary Safety, Pharmacokinetics/Pharmacodynamics, and Antitumor Activity of XmAb®20717, a PD-1 x CTLA-4 Bispecific Antibody, in Patients With Advanced Solid Tumors

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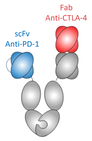
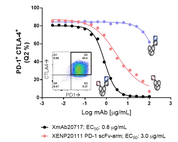
BACKGROUND

XmAb20717 Binds Preferentially to PD-1/CTLA-4 Dual-Positive Cells

PD-1 x CTLA-4 antibody XmAb20717



Avid XmAb20717 dual binding with single-domain affinity PD-1 > CTLA-4

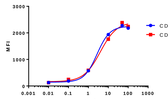


- XmAb20717, EC_{50}: 0.8 µg/mL
- XENP20111 PD-1 scFv-xmt; EC_{50}: 3.0 µg/mL
- XENP20099 CTLA-4 Fab-xmt; EC_{50}: ND

XmAb20717 is a heterodimeric antibody with a modified Fc domain that eliminates FcγR interactions and Xtend™ technology promotes longer half-life.

XmAb20717 receptor occupancy (RO) measured on PD-1/CTLA-4 transfected 239T. RO is dominated by the PD-1 arm, but greater avid binding occurs with engagement of both arms.

XmAb20717 Binding to PD-1+ SEB Stimulated PBMCs

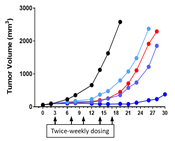


	CD4+	CD8+
EC50	2.7	4.0

XmAb20717 starting concentration = 100 µg/mL, serially diluted and detected with anti-human IgG-APC.

Binding to SEB-activated human PBMCs demonstrates comparable binding to CD4 and CD8 T cells, EC50 of 2.7 and 4.0 µg/mL, respectively.

MC38 Syngeneic Mouse Tumor Model



XmAb20053, a non-depleting PD-1xCTLA-4 mouse surrogate IgG for XmAb20717, shows dose-dependent TGI with maximum effect at 10 mg/kg in an MC38 mouse syngeneic tumor model. The 10 mg/kg XmAb20053 dose was superior to nivolumab at a clinically relevant therapeutic dose of 3 mg/kg.

- XmAb20717 is a humanized bispecific monoclonal antibody that simultaneously targets PD-1 and CTLA-4.
- DUET-2 (XmAb20717-01) is an ongoing, Phase 1, first-in-human, multicenter study, designed to evaluate the safety, pharmacokinetics (PK), pharmacodynamics, and preliminary clinical activity of XmAb20717.
- It is a 3+3 dose-escalation design, with multicohort, parallel-group expansion at the maximum tolerated dose (MTD) or recommended dose in patients with selected advanced solid tumors.
- We report preliminary data, based on a 30 September 2020 data cut.

Study Objectives

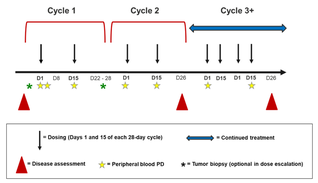
- Primary
  - To determine the safety and tolerability profile and the MTD or recommended dose of XmAb20717 for further evaluation
- Secondary
  - To characterize the PK and immunogenicity of XmAb20717
  - To assess antitumor activity, based on objective response and best overall response rates (RECIST 1.1), duration of response, and progression-free survival
- Key exploratory
  - To characterize the pharmacodynamics of XmAb20717, based on post-dosing changes in immune activity in peripheral blood and tumor
  - To evaluate the correlation between response to treatment and
    - Tumor mutational burden
    - Gene expression signatures

METHODS

XmAb20717 is administered as a 1-hour intravenous infusion on Days 1 and 15 of each 28-day cycle

XmAb20717 Dose Levels for Escalation Phase

Cohort	Dose Level (mg/kg)
1	0.15
2	0.3
3	1.0
4	3.0
5	6.0
6	10.0
7	15.0
8	20.0



Key Entry Criteria

Inclusion	Exclusion
• Histologically or cytologically confirmed eligible solid tumor – Dose escalation – tumor types with FDA-approved ICIs or published evidence of IC2 antitumor activity – Dose expansion – melanoma, RCC, NSCLC, CRPC, and a basket of other solid tumors with published evidence of ICI antitumor activity, but no FDA-approved ICI • Cancer has progressed after treatment with all standard of care therapies or for whom no treatment options are available • Measurable disease (except CRPC) • Evaluable disease per PCWG3 criteria (CRPC) • Adequate tumor biopsy tissue • ECOG 0 or 1	• Ongoing anticancer therapy (luteinizing hormone-releasing hormone analogue therapy permitted for CRPC patients) • Anti-CTLA-4 antibodies within 6 weeks or anti-PD-1 or anti-PD-L1/PD-L2 antibodies within 4 weeks prior to initiation of XmAb20717 • Grade 4 immune-mediated adverse event related to prior immunotherapy • Active known or suspected autoimmune disease* • Known active CNS metastases or carcinomatous meningitis • Estimated creatinine clearance < 30 mL/minute

*Exceptions include: vitiligo; type 1 diabetes mellitus or residual hypothyroidism due to autoimmune condition treatable with hormone replacement therapy only; autoimmune skin conditions managed without systemic therapy; arthritis managed without systemic therapy beyond oral acetaminophen and NSAIDS.
CRPC = castrate-resistant prostate cancer; ICI = immune checkpoint inhibitor; NSCLC = non-small cell lung cancer; PCWG3 = Prostate Cancer Working Group 3; RCC = renal cell carcinoma

RESULTS

Patient Disposition

	Escalation	Melanoma	RCC	NSCLC	CRPC	Basket	10 mg/kg*	Overall
Safety population, n†	34	20	11	20	18	20	96	123
Evaluable population, (%)‡	20 (58.8)	7 (35.0)	4 (36.4)	13 (65.0)	4 (22.2)	10 (50.0)	42 (43.8)	58 (47.2)
Treatment ongoing	1 (2.9)	1 (5.0)	5 (45.5)	1 (5.0)	12 (66.7)	5 (25.0)	24 (25.0)	25 (20.3)
Discontinued treatment, n (%)	33 (97.1)	19 (95.0)	6 (54.5)	19 (95.0)	6 (33.3)	15 (75.0)	72 (75.0)	98 (79.7)
Reason for discontinuation, n (%)								
Progressive disease	18 (52.9)	10 (50.0)	2 (18.2)	13 (65.0)	1 (5.6)	8 (40.0)	35 (36.5)	52 (42.3)
Adverse event	9 (26.5)	5 (25.0)	3 (27.3)	4 (20.0)	2 (11.1)	5 (25.0)	23 (24.0)	28 (22.8)
Withdrawal by subject	2 (5.9)	1 (5.0)	1 (9.1)	1 (5.0)	2 (11.1)	1 (5.0)	6 (6.3)	8 (6.5)
Other§	1 (2.9)	3 (15.0)	0	1 (5.0)	1 (5.6)	0	5 (5.2)	6 (4.9)
Physician decision	2 (5.9)	0	0	0	0	0	1 (1.0)	2 (1.6)
Missing	1 (2.9)	0	0	0	0	1 (5.0)	2 (2.1)	2 (1.6)

*Includes patients treated with 10 mg/kg in the dose-escalation phase and all patients treated in the dose-expansion phase
†Patients who receive ≥ 1 dose of XmAb20717.
‡Patients who receive ≥ 4 doses of XmAb20717 and have ≥ 1 post-baseline RECIST assessment (denominator is the Safety Population).
§Death due to disease progression – n = 3; start other anticancer therapy – n = 2; put on hospice care – n = 1.

Patients were considered evaluable for clinical activity if they had received ≥ 4 doses of XmAb20717 and had ≥ 1 follow-up RECIST assessment. Evaluation of efficacy is pending in 12 of 24 patients who were continuing treatment at the 10 mg/kg dose (8 CRPC, 3 RCC, and 1 basket cohort) because they had not met either or both of these criteria as of the cut-off date.

Demographics and Baseline Characteristics

	Escalation (n = 34)	10 mg/kg (n = 96)	Overall (n = 123)
Age, median (range)	56.5 (32-81)	65.5 (40-85)	63 (32-85)
Male, %	58.8	63.5	64.2
ECOG 1, %	67.6	62.5	64.2
Months since initial diagnosis, median (range)	42.3 (3-313)	50.2 (6-511)	46.2 (3-511)
Lines of prior systemic therapy, median (range)	4 (0-9)	4 (0-11)	4 (0-11)
Prior treatment with checkpoint inhibitor regimen, %	76.5	56.3	61.0
≥ 2 prior checkpoint inhibitor regimens, %	23.5	24.0	24.4

Data cut – 30 September 2020

Data on response to most recent prior ICI therapy were available for 33* of 54 patients treated with 10 mg/kg XmAb20717 for whom prior ICI treatment was reported. Best overall response to last prior ICI was partial response (PR) for 6.1%, stable disease (SD) for 24.2%, and progressive disease (PD) for 69.7% of patients.

*Including 11/38 patients with melanoma, 12/15 with NSCLC, 5/8 with RCC, 2/3 with cervical cancer, 1/3 with ovarian cancer, 1/1 with TNBC, and 1/1 with head and neck SCC.

Primary Tumor Types in Dose Escalation

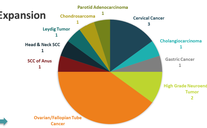
Cohort	Number of Patients
Melanoma	7
Head & neck SCC	7
Gastric cancer	5
RCC	4
TNBC	4
NSCLC	3
Cervical cancer	1
CRC (MSI-H/MMRD)	1
HCC	1
Urothelial carcinoma	1

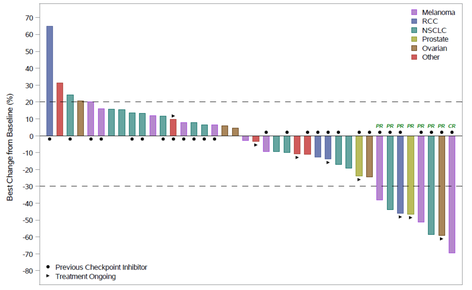
CRC = colorectal cancer; MMRD = mismatch repair deficient; HCC = hepatocellular carcinoma; MSI-H = microsatellite instability-high; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCC = squamous cell carcinoma; TNBC = triple negative breast cancer

- 34 patients were treated at 5 dose levels (0.15 to 10.0 mg/kg) in dose escalation
  - An MTD was not defined
  - Enrollment is continuing in dose escalation, currently at the 15 mg/kg dose level (data not reported)
- A dose of 10 mg/kg was identified as the recommended dose for expansion, based on
  - An observation of consistent proliferation of both CD8+ and CD4+ T cells, indicative of dual checkpoint blockade
  - A complete response (CR) in 1 patient treated in the dose-escalation phase
- 89 patients have been treated in parallel cohorts in the expansion phase as of the cut-off date

Primary Tumor Types in Dose Expansion

Cohort	Number of Patients
Melanoma	20
RCC	11
NSCLC	20
CRPC	18
Basket	20





Best percent change from baseline in sum of diameters for evaluable patients treated with 10 mg/kg. "Other" includes cervical cancer, cholangiocarcinoma, gastric cancer, and high-grade neuroendocrine tumor.

Best Overall Response (RECIST 1.1) – Evaluable Patients

	< 10 mg/kg (n = 16)	10 mg/kg (n = 42)
Best overall response, n (%)		
CR	0	1 (2.4)†
PR	0	7 (16.7)†
SD	12 (75.0)	20 (47.6)
PD	4 (25.0)	14 (33.3)
Objective response rate	NA	19.0%
Duration of response (days), median (95% CI)	NA	119.0+ (59.0, 128.0)
Disease control rate	75.0%	66.7%

†CR – confirmed; PRs – 2 confirmed

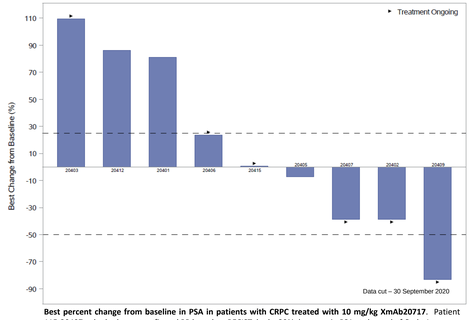
Data cut – 30 September 2020

At doses below 10 mg/kg, the best overall response was SD. At 10 mg/kg, complete and partial responses were observed in multiple tumor types, including melanoma (3 of 10 patients), RCC (1 of 4), NSCLC (2 of 14), CRPC (1 of 4), and ovarian cancer (1 of 5).

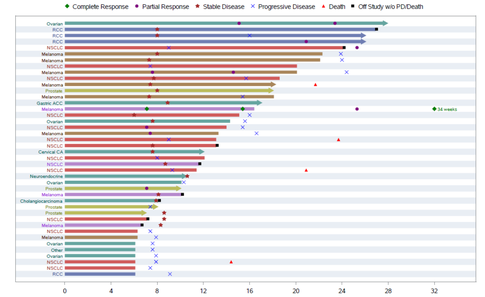
Characteristics of XmAb20717 Responders

Patient	Tumor Type	Baseline Tumor Characteristics: PD-L1 (% TPS)	Baseline Tumor Characteristics: TMB (Mut/Mb)	Prior Immune Checkpoint Inhibitor Experience: ICI	Time on Treatment (weeks)	Treatment Setting	Best Overall Response	Time From Prior ICI to Start of XmAb20717 (weeks)	XmAb20717 Response Characteristics: Best Overall Response	Time to Response (weeks)
138-10606	Melanoma	UA	UA	Pembrolizumab	19.4	Metastatic	PD	4.1	CR (C)	7.1
138-20102	Melanoma	UA	UA	Ipilimumab + Pembrolizumab	12.6	Neo-adjuvant	PD	45.6	PR (UC)	7.4
136-20119	Melanoma	0	0.8	Ipilimumab	6.1	Adjuvant	UK	111.1	PR (C)	7.6
				Nivolumab	7.4	Adjuvant	UK	86.3		
139-20303	NSCLC	2	UA	Nivolumab	28.3	Adjuvant	UK	181.7	PR (UC)	25.3
136-20318	NSCLC	40	UA	Nivolumab	20.4	Metastatic	PD	153.7	PR (UC)	7.1
				Pembrolizumab	47.9	Metastatic	SD	12.0		
136-20501	Ovarian	5	9.4	Nivolumab	2.1	Metastatic	UK	35.9	PR (C)	15.1
136-20207	RCC	0	6.3	Ipilimumab + Nivolumab	9.1	Metastatic	PD	42.9	PR (UC)	20.9
115-20407	CRPC	UA	UA	None	NA	NA	NA	NA	PR (UC)	7.1

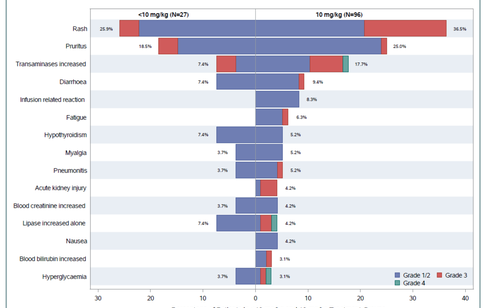
C = confirmed; UC = unconfirmed; UK = unknown; NA = not applicable; UA = unavailable



Best percent change from baseline in PSA in patients with CRPC treated with 10 mg/kg XmAb20717. Patient 115-20407, who had an unconfirmed PR based on RECIST, had a 39% decrease in PSA at the end of Cycle 1.



Time on treatment and best overall response for evaluable patients treated with 10 mg/kg. Right arrow indicates treatment is ongoing.



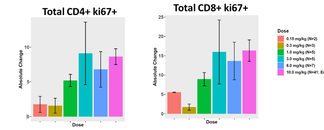
Immune-related adverse events reported for ≥ 3 patients at the 10 mg/kg dose relative to doses < 10 mg/kg by maximum CTCAE grade. Rash includes preferred terms rash maculo-papular, rash, rash macular, rash pruritic, rash pustular. Transaminases increased includes preferred terms alanine aminotransferase increased, aspartate aminotransferase increased, liver function test increased, transaminases increased.

XmAb20717 was generally well-tolerated. The most common treatment-related adverse events tended to be immune-related adverse events (irAEs).

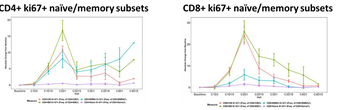
With the exceptions of rash and transaminases increased, other Grade 3 or higher irAEs were reported for ≤ 3 of 123 patients.

Neurological irAEs were reported for 2 patients and were restricted to Grade 1. Immune-related colitis was reported for 3 patients (2 Grade 3). Pneumonitis was reported for 6 patients (1 Grade 3). Immune-mediated pancreatitis (Grade 5) was reported for a single patient with RCC who had pancreatic metastases at baseline that had progressed on study. Grade 5 myocarditis and respiratory failure were reported for a patient with NSCLC who had a history of atrial fibrillation and a pacemaker. With the exception of 1 event of pneumonitis (Grade 2), all of these events were reported in patients who received the 10 mg/kg dose.

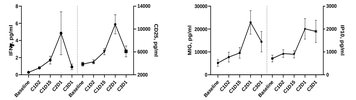
XmAb20717 Peripheral Pharmacodynamic Activity: Potent Induction of an Early Wave of T-Cell Proliferation and Th1 Cytokine Production



To evaluate peripheral pharmacodynamic activity for XmAb20717, the proliferation marker ki67 was measured in T-cell subsets by flow cytometry. Increased T-cell proliferation, in both CD4 and CD8 T cells, was observed with increasing dose, and the highest absolute change was observed at the 10 mg/kg dose.

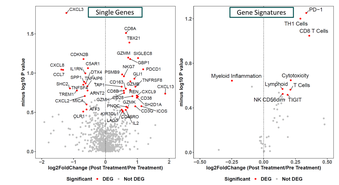


CD4 and CD8 T cells were further analyzed by gating on naïve, CM, EM and EMRA subsets. As anticipated for checkpoint inhibitor responses, the highest level of T-cell proliferation was observed in the memory compartment, specifically effector and central memory T cells. Data represent the absolute change in ki67 from baseline for all patients who received the 10 mg/kg dose.



Serum markers of T-cell activation (CD25) and IFNγ cellular responses (IFNγ and IFNγ-inducible chemokines, MIG and IP-10) are shown that demonstrate similar kinetics to ki67. Cytokine/soluble factor levels shown are the average pg/mL for each cytokine for all patients that received the 10 mg/kg dose.

XmAb20717 Intratumoral Pharmacodynamic Activity: Differentially Expressed Genes and IO360 Gene Signatures Pre- vs. Post-Treatment



Paired biopsies, collected on Cycle 1 Day 1 (pre-dose) and between Days 22 and 28 (i.e., after 2 XmAb20717 doses) were available from 15 patients. Biopsy tissue was analyzed for changes in individual genes (left panel) and gene expression signatures (right panel) using the Nanostring PanCancer IO360 Gene Expression Panel. Although on-treatment samples from clinical responders were unavailable, expected intratumoral pharmacodynamic activity was observed in this dataset, demonstrating increased expression post-treatment in genes associated with T-cell costimulation and activation (e.g., ICOS, PDCD1, GZMB, IL-2, CD28) and gene signatures demonstrating increases in T-cell infiltration and IFNγ signaling. Chemokines and other factors associated with myeloid inflammation were down-modulated on treatment. Paired biopsies were from patients with melanoma (n = 6), NSCLC (n = 3), head and neck SCC (n = 2), cervical cancer (n = 2), and ovarian cancer (n = 2), predominantly treated at 10 mg/kg (n = 13), with 1 each treated at 1 and 6 mg/kg. Best overall response for these patients was SD (n = 3), PD (n = 9), and not available (n = 3).

CONCLUSIONS

Evaluation of efficacy and safety are continuing in this ongoing study of patients with advanced solid tumors. Based on these preliminary data, XmAb20717

- Demonstrated clinical activity in multiple tumor types, including ≥ 10% tumor shrinkage from baseline in roughly half of evaluable patients and complete and partial responses, nearly all of which occurred in patients who had been exposed to prior ICI therapy
- Has been generally well tolerated at doses as high as 10 mg/kg, without exceeding the MTD
  - With the exceptions of rash and transaminases increased, other Grade 3/4 irAEs were reported for ≤ 3 of 123 patients
- Exhibited dose proportional PK, with a half-life of 7 days, and a potential association between C_{max}/AUC and clinical response
- Induced robust, dose-dependent T-cell proliferation and activation in peripheral blood consistent with dual-checkpoint blockade, peaking at Cycle 2, Day 1
- Showed expected intratumoral pharmacodynamic activity in available paired biopsies, with increases in T-cell infiltration and activation gene signatures

These encouraging preliminary results will inform further clinical development of XmAb20717 in specific oncology indications.

Many thanks for support in the conduct of this research to the patients, their families and caregivers, and the XmAb20717-01 investigational study teams.